Paper No. 40

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte GEOFFREY M. WAHL and STEPHEN O'GORMAN

Appeal No. 1996-3579
Application No. 08/147,912[1]

ON BRIEF

Before WINTERS, WILLIAM F. SMITH, and SPIEGEL, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

ON REMAND TO THE EXAMINER

Our consideration of this appeal leads us to conclude that this case is not in condition for a decision on appeal. Accordingly, we remand the application to the examiner to consider the following issues and to take appropriate action.

[1] Application for patent filed November 3, 1993. According to appellants, this application is a continuation of application 07/666,252 filed March 8, 1991, now abandoned.

1. Background

Generally, a site-specific recombinase system consists of (1) a specific enzyme, i.e., a site-specific recombinase, which will catalyze a recombination reaction only between two site-specific recombination sequences, and (2) a pair of DNA sequences, i.e., the site-specific recombination sequences. Depending upon the orientation of the site-specific recombination sequences, intervening sequences will either be excised or inverted in the presence of the site-specific recombinase. When the site-specific recombination sequences are oriented in opposite directions relative to one another, i.e., inverted repeats, then any intervening sequences will be inverted relative to the other sequence in the genome. If, however, the site-specific recombination sequences are oriented in the same direction, i.e., direct repeats, any intervening sequences will be deleted upon interaction with the site-specific recombination. See generally, Sauer.[2]

Sauer describes the Cre/lox site-specific recombinase system of bacteriophage P1, wherein "lox" refers to the DNA sequence whereat the Cre recombinase catalyzes a site-specific recombination reaction (c. 3, ll. 56-62; c. 6, ll. 6-23), i.e., (1) deletion of the DNA segment located between two lox sites in the same orientation on the same DNA molecule, (2) inversion of the nucleotide sequence of the DNA segment located between two lox sites in opposite orientation on the same DNA molecule, and (3) reciprocal

[2] Sauer, U.S. Patent No. 4,959,317, issued September 25, 1990.

exchange of DNA segments proximate to lox sites located on two different DNA molecules (c. 6, ll. 6-21).

2. Appellants' invention

Appellants' invention uses a FLP/FRT site-specific recombinase system to remove or insert DNA into specific sites in mammalian chromosomes (specification, p. 4, ll. 7-30). FLP recombinases are derived from Saccharomyces yeast and the FLP site-specific recombination site, i.e., the FLP recombination target site or "FRT," has been identified as minimally comprising two 13 base-pair repeats, separated by an 8-base-pair spacer, e.g., 5'-GAAGTTCCTATTC[8-base spacer]GTATAGGGAACTTC-3' (specification, p. 11, ll. 10-35). Claims 25, 26 and 42 are illustrative and read as follows.

> 25. A method for precisely targeting integration of a nucleic acid into the genome of a mammalian host cell, said method comprising:
> (i) stably integrating a first nucleic acid comprising a FLP recombination target site (FRT) into the genome of said mammalian host cell,
> (ii) introducing into said mammalian host cell of step (i) a second nucleic acid comprising at least one FRT along with an FLP recombinase, wherein said FLP recombinase catalyzes recombination between the integrated FRT and the FRT of said second nucleic acid, thereby precisely targeting integration of said nucleic acid into the genome of said mammalian host cell of step (i).
>
> 26. A method for excising a second nucleic acid that has been integrated into the genome of a mammalian host cell according to the method of Claim 25, comprising contacting the genomic DNA of said

> mammalian host cell with an FLP recombinase, wherein the FLP recombinase catalyzes recombination of the FRT of said first nucleic acid and the FRT of said second nucleic acid, thereby excising the integrated second nucleic acid from the genome of said mammalian host cell.
>
> 42. A method for the site-specific integration of a nucleic acid into the genome of a mammalian cell wherein at least one FRT is stably integrated in the genome of said mammalian cell, said method comprising:
> introducing into said mammalian cell a first nucleic acid comprising at least one FRT and at least a first partial coding sequence of a first gene of interest, along with an FLP recombinase, wherein the FLP recombinase catalyzes recombination between the integrated FRT and the FRT of said first nucleic acid, thereby specifically integrating said first nucleic acid at the site of FRT recombination in said genome of the mammalian cell.

3. Claim interpretation and the grounds of rejection

Our appellate reviewing court stated in Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-68, 1 USPQ2d 1593, 1597 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987):

> Analysis begins with a key legal question -- what is the invention claimed? Courts are required to view the claimed invention as a whole. 35 U.S.C. § 103. Claim interpretation, in light of the specification, claim language, other claims, and prosecution history, is a matter of law and will normally control the remainder of the decisional process. [Footnote omitted.]

Here, such an inquiry is essential to determining issues of written descriptive support, enablement, definiteness, novelty and obviousness.

The examiner has rejected (1) claims 25, 26, 28, 42-46 and 48 under 35 U.S.C. § 112, first paragraph, because the specification fails to provide a reasonable written

description and enablement for practicing the claimed invention,[3] (2) claims 25, 26, 28, 42-46 and 48 under 35 U.S.C. § 112, first paragraph, as not enabled for precisely targeting the first FLP recombination target site to a predetermined site of integration, (3) claims 25, 26, 28, 42-46 and 48 under 35 U.S.C. § 112, second paragraph, as indefinite, (4) claims 25 and 28 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Golic,[4] (5) claims 25, 26, 28, 42-46 and 48 under 35 U.S.C. § 103 as being unpatentable over Sauer taken with Golic, and (6) claims 25, 26 and 28 under 35 U.S.C. § 103 as being unpatentable over Sauer taken with Golic as applied to claims 25, 26, 28, 42-46 and 48 above, and further in view of Palmiter.[5]

a. rejection of claims 25, 26, 28, 42-46 and 48 under § 112, ¶2, as indefinite

The examiner finally rejected specific claims or sets of claims having an alleged common defect (i.e., claims 25, 26, 28, 42, 43, 44 and /or 48) as indefinite under § 112, second paragraph (Paper No. 26, mailed July 14, 1994, pp. 3-4). Appellants' response in

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[3] In the final rejection claims 25, 26, 28, 42-46 and 48 were rejected under 35 U.S.C. § 112, first paragraph, for failure to provide the best mode as well. Insofar as the best mode rejection is not repeated in the answer, it is presumed to have been withdrawn. Ex parte Emm, 118 USPQ 180, 181 (Bd. App. 1957).

[4] Golic et al. (Golic), "The FLP Recombinase of Yeast Catalyzes Site-Specific Recombination in the Drosophila Genome," Cell, Vol. 59, pp. 499-509 (November 1989).

[5] Palmiter et al. (Palmiter), "Germ-line Transformation of Mice," Ann. Rev. Genetics, Vol. 20, pp. 459-99 (1986).

toto in both the "defective" brief[6] filed July 20, 1995 (Paper No. 31, pp. 6-7) and the "corrected" brief filed October 2, 1995 (Paper No. 35, hereinafter "brief," pp. 8-9) was that

> [t]he Examiner's assertion that claims 25, 26, 28, 42-46 and 48 are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as invention is respectfully submitted to be in error for the following reasons. The Examiner's concern with precise targeting of the first DNA is respectfully submitted to be misplaced. As discussed above, the invention process occurs in two steps. First, a FLP recombination target site is introduced, then a nucleic acid is precisely targeted and integrated at the previously introduced FLP recombination target site.
>
> The proposed amendments to claim 42, as submitted herewith, as part of the Amendment After Final, render moot the concern that reference to "nucleic acid" in the preamble of the claim refers to both the first and second nucleic acids. It is respectfully submitted to be clear that the precise targeting contemplated by the present claims is accomplished in the FLP recombinase-promoted step.

First, the proposed amendment to claim 42, originally filed July 20, 1995 in an **AMENDMENT AFTER FINAL** (Paper No. 32) concurrently with the defective brief (Paper No. 31), was not entered by the examiner (see the advisory action mailed August 24, 1995 (Paper No. 33)). The later filed brief failed to either acknowledge or respond to the non-entry to the earlier proposed amendment to claim 42.

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[6] A "NOTIFICATION OF NON-COMPLIANCE WITH 37 CFR 1.192(c)" was mailed September 1, 1995 (Paper No. 34). A brief correcting the defects listed in the notification was filed October 2, 1995 (Paper No. 35).

Next, the examiner repeated each individual rejection under §112, second paragraph, set forth in the final rejection in the answer (Paper No. 36, mailed December 12, 1995, pp. 7-8) and stated that

> ...the claims (e.g., claim 25) require "precise" targeting and even as argued in the brief, it does not show nor demonstrate how the first nucleic acid FLP recombination target site is precisely targeted since as presently recited, the claim also calls for precise targeting of the first DNA as the "a nucleic acid" refers to both the first and second DNA fragments whereas appellant argues that does not, however, appellant's amendment's to the claims do not reflect appellant's statements in the brief. ... Discussion of the unentered amendment is not persuasive nor applicable to claims on appeal not containing that amendment. [Answer, p. 12.]

Appellants' acknowledged the non-entry of the July 20, 1995 amendment[7] in their reply brief (Paper No. 37, filed February 16, 1996, p. 4) without further comment.

The legal standard for definiteness under 35 U.S.C. § 112, second paragraph, is whether a claim reasonably apprises those of skill in the art of its scope. In re Warmerdam, 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1759 (Fed. Cir. 1994). "[D]efiniteness of the language employed must be analyzed, not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be reasonably interpreted by one possessing the ordinary level of skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

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[7] The file of this application lists July 20, 1995 as the filing date of Paper No. 32, although the actual paper contains a certification of mailing July 17, 1995 in the upper right-hand corner of its first page. Our reference to filing and mailing dates of various papers is that of the dates listed on the front of the application file.

The record presently before us contains rejections (1) which are conclusory in nature, e.g., both the first and second DNA fragments must be precisely targeted, (2) which suggest that required parameters are missing from the claims, e.g., FLP recombinase cannot run forwards (i.e., produce the insertion product of claim 25) and backwards (i.e., produce the excision product of claim 26) under the same conditions but for dynamic equilibrium, (3) which question the relationship between the various reactants, e.g., which DNA segments recombine where three separate FRTs are present as in claim 28, and (4) which question the definition of terms, e.g., what defines a "partial" coding sequence as recited in claim 44 (see answer, pp. 7-8), on the one hand and little, if any, response from appellants on the other hand. This is an inadequate basis upon which to determine how the claimed invention would be reasonably interpreted by one possessing the ordinary level of skill in the pertinent art. We are a board of review, not a panel of de novo examination. Consequently, in our view, it is premature to address the merits of the various rejections under 35 U.S.C. § 112, second paragraph.

b. rejections claims under § 112, first paragraph, § 102 and § 103

While we might speculate as to what is meant by the claim language, our uncertainty provides us with no proper basis for making the comparison between that which is claimed and the prior art as we are obliged to do. Rejections under 35 U.S.C. § 102 and § 103 should not be based upon "considerable speculation as to the meaning of terms employed and assumptions as to the scope of the claims." In re Steele, 305 F.2d

859, 862, 134 USPQ 292, 295 (CCPA 1962). Similarly, a claim which is indefinite under the second paragraph of 35 U.S.C. § 112 cannot even be analyzed under the first paragraph of 35 U.S.C. § 112, because that analysis could not be carried out unless one was able to determine exactly what subject matter the claim encompassed. This same proposition can be found at least strongly implicit in the decisions in Moore and In re Merat, 519 F.2d 1390, 186 USPQ 471 (CCPA 1975). In Moore, the court first determined whether the subject matter defined by the claims was particular and definite before turning to the first paragraph of section 112 to determine "whether the subject matter defined in the claims is described in the specification, whether the specification disclosure as a whole is such as to enable one skilled in art to make and use the claimed invention, and whether the best mode contemplated by the inventor of carrying out the invention is set forth." Id., 439 F.2d at 1234, 169 USPQ at 238. In Merat, the court stated that its affirmance of the 35 U.S.C. § 112, second paragraph, rejection rendered it "unnecessary to discuss the other grounds of rejection," which included rejections under 35 U.S.C. §§ 101 and 103. Id., 519 F.2d at 1393, 186 USPQ at 474. Accordingly, it is premature to reach the merits of the rejections under 35 U.S.C. §§ 112, first paragraph, 102 and 103.

4. Observations

a. rejections based on anticipation and obviousness

Anticipation requires that all elements of the claimed invention be described, either expressly or under the principles of inherency, in a single prior art reference. In re

Paulsen, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); In re Spada, 911 F.2d 705, 708, 15 USPQ2d 2d 1655, 1657 (Fed. Cir. 1990). Therefore, the examiner should point out where each and every claim limitation is described, either expressly or implicitly. For example, the examiner should point where Golic describes stable integration of a first FRT and introduction of at least one additional FRT (as required by claim 25) and clarify whether these steps occur simultaneously or sequentially. The examiner should point out where Golic describes introduction of a third FRT (as required by claim 28). The examiner should explain why one skilled in the art reading the disclosure in Golic that "we expect that it [the FLP recombinase system] will work in other organisms as well" (p. 507, c. 2, para.3) would have readily envisaged that "other organisms" meant mammalian cells as opposed to some other type of eukaryotic cells. See In re Schaumann, 572 F.2d 312, 316, 197 USPQ 5, 9 (CCPA 1978).

As to obviousness, the examiner has the initial burden of establishing a prima facie case of obviousness. In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ 1955, 1956 (Fed. Cir. 1993). In rejecting a claim under 35 U.S.C. § 103, the examiner must provide a factual basis to support the obviousness conclusion. In re Freed, 425 F.2d 785, 788, 165 USPQ 570, 572 (CCPA 1970). Based on the objective evidence of record, the examiner is required to make the factual inquiries mandated by Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 469 (1966). The examiner is also required to explain why one having ordinary skill in the art would have been led to modify and/or combine the applied

prior art to arrive at the claimed invention. To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from knowledge generally available to one of ordinary skill in the art and not from the appellant's disclosure. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988), cert. denied, 488 U.S. 825 (1988); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 293, 227 USPQ 657, 664 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). These showings by the examiner are an essential part of complying with the burden of presenting a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Therefore, the examiner should point out where the reference(s) applied under 35 U.S.C. § 103 disclose(s) or suggest(s) all the claim limitations, provide(s) some suggestion or motivation to modify the reference to obtain appellant's claimed invention and a reasonable expectation of success in doing so.

For example, the examiner asserts that the Cre/lox and FLP/FRT recombination systems "have the same/analogous features, characteristics, and properties" (answer, p. 16) without explaining what he is specifically referring to and presumably why these same/analogous factors would have provided a reasonable expectation of success in substituting the FLP/FRT system of Golic for the Cre/lox system of Sauer in order to obtain site-specific recombination in mammalian host cells. The examiner is reminded

that

> ... "obvious to try" is not the standard under § 103 [and is] ... directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted).

Finally, the examiner should explain the relationship between mitotic recombination, i.e., "mating the flies," in Golic (answer, p. 15) and (a) the claimed invention and (b) appellants' arguments directed to homologous and heterologous DNA interactions (see e.g., brief, pp. 10-11).

b. rejections under §112, ¶1, lack of written description and enablement

A specification complies with the description requirement of 35 U.S.C. § 112, first paragraph, if it conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention. The examiner has the initial burden of establishing a prima facie case of lack of an adequate written description. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976).

A specification complies with the enablement requirement of 35 U.S.C. § 112, first paragraph, if it allows one of ordinary skill in the art to make and use the claimed invention without undue experimentation and, again, the examiner has the initial burden of

establishing lack of enablement. In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). As set forth In re Wands, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered In determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those In the art, the predictability or unpredictability of the art, and the breadth of the claims.

The examiner should begin his analysis of the claimed invention with this background. For example, assuming arguendo, that the claimed invention does not require a first nucleic acid comprising a FRT to be integrated In a site-specific manner into the genome of a mammalian host cell, the examiner should consider whether the specification, e.g., at p. 15, ll. 4-9, would enable one of ordinary skill In the art to stably integrate such a first nucleic acid into the genome of the mammalian host cell. Appellants refer to Example 1, pp. 17-22 as showing the introduction of the initial FRT (brief, p. 7). However, Example 1 does not show FLP recombinase mediating a subsequent integration of a second nucleic acid comprising at least one FRT between the integrated FRT of the first nucleic acid and the FRT of the second nucleic acid. Rather Example 1 shows cutting the first nucleic acid In the middle of its FRT site and then inserting a second nucleic acid containing a "NEO" DNA segment flanked by two half-FRT sits so as to create intact FRTs

on either side of the "NEO" DNA segment (specification, p. 18, ll. 21-26). It appears that specification Example 3, entitled "FLP-Mediated Recombination of FRT on an Extrachromosal Molecule With a Chromosomally Integrated FRT" (pp. 25-27), is more germane to the subsequent site-specific integration of nucleic acid sequences. However, Example 3 has not been discussed by either appellants or the examiner. The examiner should explain how Example 3 supports his position that the initial, i.e., chromosomally integrated, FRT must be precisely placed In the genome. Finally, the examiner should consider whether the specification explains the difference between (a) chromosomal integration of FRT, (b) inverting or excising a DNA segment between two flanking FRTs, and (c) integrating (i.e., exchanging? or mating?) DNA segments proximate to lox sites located on two different DNA molecules. It may be that the specification describes and enables excisional recombination but not the reverse. Reversal of excisional recombination may require different experimental conditions, which may or may not be reproducibly predictable.

c. issuance of divisional applications

We have become aware of two patents which have issued from divisional applications of the application on appeal, i.e., US Patents 5,654,182 (Application No. 08/484,324) and 5,677,177 (Application No. 08/486,409). The first issued claim in each of these patents, respectively, read as follows.

1 ('182). A method for the integration of a first nucleic acid into the genome of a mammalian host cell, said method comprising:

a) stably integrating a first FLP recombination target site (FRT) into said genome; and

b) introducing into said mammalian host cell of step a) an FLP recombinase and said first nucleic acid, wherein said first nucleic acid comprises a second FRT, and wherein said FLP recombinase catalyzes recombination between said first FRT and said second FRT, thereby precisely targeting integration of said first nucleic acid into said genome at the site of said first FRT, thereby achieving the assembly or disassembly of a functional expression unit.

1 ('177). A composition that effects recombination In mammalian cells comprising:

(i) an isolated and purified FLP recombinase, or an isolated and purified nucleotide sequence encoding the same, and

(ii) a first DNA comprising a nucleotide sequence containing a first FLP recombination target site (FRT) therein,

wherein the genome of the mammalian cells contains a stably integrated second FRT site, and wherein said FLP recombinase catalyzes a recombination between said first FRT and the second FRT, thereby precisely targeting integration of said first DNA into the genome.

The examiner should review the prosecution history of each of these two related applications. The examiner should consider whether there is any difference between "precisely targeting integration" as recited in the claimed invention on appeal and "precisely targeting integration" as recited in the '182 and '177 patents; and, the basis for allowance of the '182 and '177 patents.

We note the MPEP § 1003 states in pertinent part that matters pertaining to an

> 6. Action which hold unpatentable claims copied from a patent for interference purposes where the grounds relied upon are equally applicable to the patentee, MPEP § 2307.02

should be submitted to the appropriate Group Director, together with a reference to any section of the MPEP where the matter is more fully treated. MPEP § 2307.02 reads In part

> When claims corresponding to claims of a patent are presented, the application is taken up at once and the examiner must determine whether the presented claims are unpatentable to the applicant on any ground(s), e.g., under 35 U.S.C. 102, 35 U.S.C. 103, 35 U.S.C. 112, 35 U.S.C. 135(b), double patenting, etc. If at least one of the presented claims is not rejectable on any such ground and is claiming the same invention as at least one claim of the patent, the examiner should proceed to initiate an interference.
>
> If all of the claims presented are rejectable on any grounds, they should be so rejected. The ground of rejection of the claims presented may or may not be one which would also be applicable to the corresponding claims In the patent. <u>If the ground of rejection is also applicable to the corresponding claims In the patent, any letter including the rejection must have the approval of the Group Director. See MPEP § 1003.</u> [Emphasis added.]

Therefore, any ground of rejection raised in the present application on appeal which is also applicable to any claims in the issued '182 and '177 patents would appear to need the approval of the Group Director.

d. <u>point-by-point rebuttal</u>

According to MPEP § 1206,

> Where an appeal brief fails to address any ground of rejection, appellant shall be notified by the examiner that he or she must correct the defect by filing a brief (In triplicate) In compliance with 37 CFR 1.192(c). ... The fact that appellant may consider a ground to be clearly improper does not justify a failure to point out to the Board the reasons for that belief.

Thus, the examiner should have notified appellants that their brief did not contain, for each rejection under 35 U.S.C. § 112, second paragraph, i.e., for each claim/claim set rejection, an argument which specified the errors in the rejection and how the claims particularly point out and distinctly claim the subject matter which appellants regarded as their invention.[8] Under 37 CFR § 1.192(c)(8), appellants' arguments must address each rejection whether under 35 U.S.C. § 112, 35 U.S.C. § 102, 35 U.S.C. § 103, or other grounds. Both the examiner and appellants are cautioned that failure to present a point-by-point rebuttal to each rejection leads to an inference that one party has acquiesced to the position of the other party.

[8] The examiner did specifically notify appellants that their "brief on appeal contains no arguments traversing the above indicated ground of rejection [i.e., "[t]he rejection of claims 25, 26 and 28 under 35 U.S.C. 103 as being unpatentable over Sauer (U.S. '317) taken with Golic et al. as applied to claims 25, 26, 28, 42-46 and 48 above, and further In view of Palmiter et al.] (answer, para. bridging pp. 16-17).

5. Closing

This application, by virtue of its "special" status, requires an immediate action. MPEP § 708.01(D)(7th ed., rev. 1, February 2000).

REMANDED

SHERMAN D. WINTERS
Administrative Patent Judge

WILLIAM F. SMITH
Administrative Patent Judge

CAROL A. SPIEGEL
Administrative Patent Judge

) BOARD OF PATENT APPEALS AND INTERFERENCES

CAS/cam

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